REMARKS

Claims 1-11 and 13-16 are pending in this application. Claims 1-5, 7-9, and 15-16 have been amended. New claims 17-20 have been added. No new matter has been introduced. Claims 1-5, 7-9, and 15-16 have been amended for the following reasons:

claim 1 - to identify the CpG oligonucleotide as an immunostimulatory CpG oligonucleotide containing an unmethylated CpG dinucleotide, and to identify the fusion partner as a fusion partner having T helper epitopes in order to better define the metes and bounds of the invention;

claim 2 - to identify the fragments as fragments that have T helper epitopes in order to better define the metes and bounds of the invention;

claim 3 - to delete the term "derived" in order to better define the metes and bounds of the invention;

claims 4 and 5 - to identify the mutation in order to better define the metes and bounds of the invention;

claim 7 - to identify the additional HPV antigens in order to better define the metes and bounds of the invention;

claims 8 and 9 and 15 - to identify the CpG oligonucleotide as an immunostimulatory CpG oligonucleotide in order to better define the metes and bounds of the invention;

claim 15 - to identify the CpG oligonucleotide as an immunostimulatory CpG oligonucleotide and to identify the fusion partner as a fusion partner having T helper epitopes in order to better define the metes and bounds of the invention;

claim 16 - to identify the additional HPV antigens in order to better define the metes and bounds of the invention.

Attached hereto is a marked-up version of the changes made to specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES".**

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Objections to the Specification

Applicants have amended the title of the invention to address the Examiner's objection.

With regard to the Examiner's objection to certain, Applicants submit that words such as "tumour" and "immunise" are in common usage and well understood in the english language as the English spellings of the American English words "tumor" and "immunize". Accordingly, Applicants respectfully request withdrawal of this objection

Applicants note that in order to bring the application in compliance with US practice, Applicants have added appropriate headings and language to the specification. No new matter has been introduced.

Rejection Under 35 USC §112, Second Paragraph - Claims 1-11, 13-16

The Examiner has rejected all claims as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.
Claims 1, 8-10 and 15 were rejected for not defining the claimed CpG oligonucleoties. While Applicants believe that CpG oligonucleotides are properly defined on page 3 lines 25-32 and on page 4 lines 1-17 of the specification as published (PCT), the claims have been amended to further define the CpG oligonucleotides as immunostimulatory CpG oligonucleotides.

Claims 1 and 15 were further rejected for failing to properly define the fusion partner. Applicants respectfully submit that claim 1 does not just contemplate any fusion partner, it specifically contemplates an immunological fusion partner (IFP). An immunological fusion partner is defined in the text (page 4, lines 18-20) as "having T helper epitopes". Applicants have amended the claims to include this limitation. Applicants further submit that the rejection of claims 1 and 15c because of the term "optionally linked to" should also be withdrawn in view of this amendment and the specification ehich clearly sets the products it refers to within the composition as being E7 or E6 or E6E7 fusion in the form or not of an IFP fusion (see the specification on page 9, lines 4-6). Furthermore, the specification makes it clear that the compositions according to the invention are compositions comprising a HPV antigen (whether linked or not to an IFP), formulated or adjuvanted with a CpG oligonucleotide (please refer to the specification as filed, on page 1, lines 5 and 12; page 4 lines 18-21).

The Examiner rejected claim 2 for containing the term "fragment thereof". Applicants amended the claims to specify that the "fragments thereof" refers to the named IFP that have T helper epitopes. Basis for this amendment can be found in the specification as filed on page 4, first paragraph.

The Examiner rejected claim 3 (Applicants assume the Examiner intended to reject claim 3 and not claim 1) for containing the term "derived". Claim 3 has been amended by deleting the word "derived".

The Examiner rejected claims 4 and 5 for failing to define the possible mutations to the E6 and E7 genes. Applicants have amended the claims to indicate that the contemplated mutations result in a change in function of the E7 and E6 protein respectively. Basis for the amendment of claim 4 (mutation in E7) can be found in the specification as filed on page 5, lines 22-24. The specific mutations disclosed on page 5, lines 24-26 are preferred embodiments, and claim 4 should not be restricted to these embodiments only. The skilled man would know from the art what residues in E7 are involved in – and disrupt - the rb binding (see Ullman, C. G. and Emery, V. C. (1996) *Reviews in Medical Virology 6(1)*:39-55). Support for the amendment of claim 5 (mutation in E6) can be found in the specification on page 5, lines 29-30. The skilled reader will know that E6 binds to and inactivates the p53 tumor suppressor protein, a result that may lead to oncogenesis (see again Ullman, C. G. and Emery, V. C. (1996) *Reviews in Medical Virology 6(1)*:39-55). A copy of the Ullman et al. article is provided to the Examiner herewith.

The Examiner rejected claims 7 and 16 for failing to define "additional HPV antigens." Applicants disagree with the Examiner's. The specification, on page 9, clearly states that other HPV antigens from HPV (strains 16 and 18, but also 6, 11, 31 or 33) are contemplated, preferably L1 and L2, and additional early antigens such as E2 and E5. Furthermore, in the background art section, the specification discloses the role of the early antigens, as well as the role of the late antigens in the carcinoma of the cervix (see pages 2 and 3). Nevertheless, in order to secure a patent in the shortest time possible, Applicants have amended claims 7 and 16 to define the additional HPV antigen is one or more antigens selected from the group consisting in E2, E5, L1 and L2.

Accordingly, Applicants respectfully request that the rejection of the claims under 35 USC §112, second paragraph, should be withdrawn.

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Rejection Under 35 USC §112, First Paragraph - Claims 1-16

The Examiner rejected claims 1-16 for not being enabled. Specifically, while the Examiner acknowledges that the specification is enabling for making a variety of compositions comprising HPV E6, E7 and E6E7 linked to an IFP, the Examiner asserts that the specification it does not enable the claims E6 or E7 optionally linked with fusion partners plus additional antigens. Applicants disagree and respectfully submit that at least two different oligonucleotides have been used in the *in vivo* experiments involving mice injected with TC1 tumour cells, CpG 1826 (oligo 1) (as mentioned by the Examiner on pages 4 and 5 of his letter) and CpG 1758 (oligo 2). The details of the experiment can be found on page 28 of the PCT application (Example XIII). As stated in the conclusion on page 29 (lines 22), "both CpG induced complete tumour regression". This can be seen in Figure 2, in Figure 5 (with as much as 4 different doses of CpG oligo 1) and in Figure 6. Additionally, these results have been obtained using two different animal models: mice having received TC1 tumour cells which then developed a growing tumour (Examples XIII and XIV), and transgenic mice expressing E7 protein from HPV16. In the latter model also, vaccination with CpG/proteinD1/3 E7 "results in a reduction of tumour growth and can induce complete tumour regression" (page 35, lines 8-10). The present application does actually **demonstrate** by the means of working examples that vaccine compositions according to the invention are effective in inducing tumour regression in HPV induced tumours. The specification further teaches that the vaccine compositions are effective in generating CTL responses, indicative of a therapeutic effect in cancer diseases, and also in inducing a TH-1 type immune response against the antigen. The same advantages of the present invention can be achieved through several CpG sequences and that in this respect CpG 1826 and CpG 1758 are contemplated to be specific, preferred, embodiments of the vaccine composition and are claimed as such in dependent claim 11.

The Examiner further states that the field of CpG oligonucleotides is unpredictable in that not every CpG motif can have immunostimulatory activity. Applicants respectfully submit that the amendments to the claims which indicate that CpG oligonucleotides contemplated herein are immunostimulatory, render this rejection moot.

The Examiner has also rejected the claims in because of the alleged unpredictability in the vaccines art. Specifically, the Examiner suggests that the term vaccine means complete protection of a host against disease, and that in order to be enabled, the claimed compositions,

methods and vaccines must confer absolute protection from disease. Applicants respectfully disagree. Vaccines are now regularly prepared to combat various diseases and they would therefore one skilled in the art understands the term to mean protection and not necessarily absolute protection. Contrary to what the Examiner suggests, there is no requirement for absolute predictability of protection and to demonstrate "*sustained immune response, complete prevention of HPV induced tumour development and long-term protection against HPV infection*". Applicants have discovered that a specific immune response (antibodies, CTL, proliferation) can be induced in several animal models after administration of the composition of the invention, and that this composition has a strong therapeutic potential in that it was effective in inducing tumour rejection or tumour growth reduction. This therapeutic potential is illustrated in Example XIII. In view of the specification and especially the examples set forth therein, Applicants respectfully submit that the amended claims are fully enabled.

With respect to the Examiner's assertion that the specification lacks teaching with respect to HPV, Applicants respectfully disagree and submit that sufficient guidance has been given to the skilled man to make the invention in respect of compositions comprising several types of HPV-derived antigens, without the need for undue experimentation. Numerous illustrative examples have been given. Furthermore, one skilled in the art would know how to actually clone and express the additional antigen, relying on basic knowledge in the field of molecular biology and protein purification. HPV genomes have been known for years, their early and late genes have been characterised and their involvement in the viral replication, transcriptional control and tumour development has been studied. This is discussed in the specification as filed on pages 2 and 3. No undue experimentation is required to practice the instant invention.

Accordingly, Applicants respectfully request the withdrawal of the rejection of the claims under 35 USC §112, first paragraph.

Rejection Under 35 U.S.C. § 103(a) – Claims 1-11 and 13-16

The Examiner rejected all claims as being obvious over Bournesell et al., Borysiewicz et al., Edwards et al., Carson et al. and Chu et al. Applicants respectfully disagree.

The Examiner gathered various elements from five separate references and determined that it would have been obvious to one skilled in the art to combine such references and arrive

at the invention as presently claimed without considering whether the references provide the necessary motivation. It is well established that to find obviousness under 35 U.S.C. §103, the scope and contents of the prior art cannot be determined by the mere gathering of elements from separate and distinct disclosures without taking into consideration the teachings of the disclosures. "The mere fact that those disclosures can be combined does not make the combination obvious unless the art also contains something to support the desirability of the combination." *In re Imperato*, 179 U.S.P.Q. 730 (C.C.P.A. 1973). There must be a reason apparent at the time the invention was made to combine the references or the use of such teachings as evidence of obviousness will entail prohibited hindsight. *In re Nomiya,* 184 U.S.P.Q. 607 (C.C.P.A. 1975). Hindsight selection of the pertinent art must be avoided. *Union Carbide Corp. v. American Can Co.*, 724 F. 2d 1567, 220 U.S.P.Q. 584 (Fed. Cir. 1984). *See also, In re Fine,* 5 U.S.P.Q. 2d. 1596 (Fed. Cir. 1988). In addition, it is improper to pick and choose, as the Examiner did, from any one reference only so much of it as will support a given position, to the exclusion of what such references suggest to one of ordinary skill in the art. *In re Hedges*, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986). When the teachings of the references, individually or collectively, are taken into consideration and there is no improper hindsight selection of various elements from the cited references, it becomes apparent that the invention as presently claimed is not obvious.

The present invention is not directed to "polynucleotide constructs consisting of the part of the coding sequence of E6 or E7 protein of E6/E7 fusion protein from HPV16 or HPV18" as asserted by the Examiner at page 6, last paragraph, of the Office Action. The present invention claims a composition comprising an E6 or E7 protein or E6/E7 fusion protein from HPV optionally linked to an immunological fusion partner having T helper epitopes, and an immunostimulatory CpG oligonucleotide containing an unmethylated CpG dinucleotide. The composition of the instant invention has been shown to induce an effective immune response against the HPV antigen, which leads to tumor regression.

Edwards et al. (WO 96/19496) disclose HPV E6 and E7 protein variants, especially deletion mutants, or fusions of deleted or full length E6 and E7. The deletions disclosed in Edwards can concern as much as 90% of the full-length E6 or E7 protein sequence (see page 7, lines 14-15). These variants are claimed to be useful in vaccines due to the fact that they are highly immunogenic (Example 5, Table 1 on page 21) and no longer cell-transforming in the host animal (Example 6, Table 2 on page 23).

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Boursnell et al. disclose the construction and characterization of a recombinant vaccinia virus expressing the E6 and E7 proteins from HPV types 16 and 18. The recombinant virus was shown to be less neurovirulent compared to the parental strain and capable of inducing an HPV-specific CTL response.

Similarly, Borysiewicz et al. report that a recombinant vaccinia virus encoding HPV types 16 and 18 E6 and E7 proteins is safe and capable of inducing HPV-specific immune responses in humans.

These three references disclose that it is possible to induce a high immune response using the E6 and E7 antigens. These references, however, do not disclose or suggest the need for further improving the effectiveness of the antigens. They certainly do not disclose the need or possibility of improving the immune response through the use of a Th1 adjuvant, let alone through the use of a CpG oligonucleotide.

Chu et al. teach that synthetic CpG oligodeoxynucleotides act as adjuvants that switch on T helper 1 (Th1) immunity thereby making them attractive adjuvant candidates for a wide range of infectious diseases and immune disorders (see page 1630, right column lines 1-3).

Carson et al (WO 97/28259) are concerned with recombinant gene expression vectors including non-coding palindromic regions of single or double-stranded DNA or RNA polynucleotides which include at least one cytosine-guanine dinucleotide motif in each palindrome. These polynucleotide regions are reported to be immunostimulatory and serve as adjuvants.

Neither Chu et al. nor Carson et al. deal with providing an effective composition against HPV-induced tumours.

None of the cited disclose compositions comprising a CpG oligonucleotide and a HPV-derived antigen. As the references do not suggest the need for HPV improved formulations they certainly do not suggest specific HPV antigens-CpG compositions to achieve such a goal. One skilled in the art would have no motivation to combine the teaching of these numerous references to address an unidentified problem. Applicants were the first to disclose such a composition and to demonstrate that it was effective in inducing a reduction or in abolishing completely an HPV-induced tumour. The first three publications discussed above do not suggest the need for an improved antigenic formulation against HPV-induced cancers, moreover they are completely silent about the use of a Th1 adjuvant in general and about the need for CpG in particular. The last two publications are completely silent about

HPV in general, and about HPV specific antigens in particular. Furthermore, contrary to the Examiner's assertion, there is no disclosure in the above references that an E7 antigen in combination with other HPV antigens have long been recognized and used as the target for developing CTL activity of the Th1 type.

Surprisingly, the present inventors have found that the claimed method and composition exhibits an unexpected synergistic effect over compositions comprising either component (the oligonucleotide and the antigen) individually. This synergistic effect is disclosed in the specification (Figures 1 and 2).

Applicants respectfully submit that the claims, as amended, are not obvious over the cited art, and respectfully request withdrawal of the rejection of the claims under 35 U.S.C. §103(a).

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES

IN THE SPECIFICATION:

The specification from page 1 to page 4, line 21 has been amended as follows:

--[VACCINE] Compositions Comprising Human Papilloma Virus Proteins and Fusion Proteins Adjuvanted with a CpG Oligonucleotide

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a 371 of PCT/EP98/08563, filed December 18, 1998, which claims priority from GB 9727262.9, filed December 24, 1997.

[The present invention relates to vaccine compositions, comprising an E6 or/ and E7 or E6, E7 fusion protein from an HPV strain optionally linked with an immunological fusion partner and formulated with a CpG containing oligonucleotide into vaccines that find utility in the treatment or prophylaxis of human papilloma virus induced tumours or lesions. In particular, the present invention relates to vaccines comprising fusions proteins, comprising a protein or part of a protein that provides T helper epitopes (such as protein D from Heamophilus influenzae B) and an antigen from a human-papilloma virus (eg comprising an E6 or E7 protein from HPV 16 or 18 strain associated with cancer) that find utility in the treatment or prophylaxis of human papilloma induced tumours, wherein the vaccine is formulated with a CpG containing oligonucleotide as an adjuvant.]

BACKGROUND OF THE INVENTION

Papillomaviruses are small naked DNA tumour viruses (7.9 kilobases, double strand), which are highly species-specific. Over 70 individual human papillomavirus (HPV) genotypes have been described. Papillomaviruses are classified on the basis of species of origin (human, bovine etc.) and of the degree of genetic relatedness with other papillomaviruses from the same species. HPVs are generally specific for the skin or mucosal surfaces and have been broadly classified into "low" and "high" risk viruses.

Low risk HPVs usually cause benign *lesions* (warts or papillomas) that persist for several months or years. High risk HPVs are associated with pre-neoplastic lesions and cancer. The strongest positive association between an HPV virus and human cancer is that which exist between HPV 16 and 18 and cervical carcinoma. More than ten other HPV types have also been found in cervical carcinomas including HPV 31 and HPV 33 although at less frequency.

Genital HPV infection in young sexually active women is common and most individuals either clear the infection, or if lesions develop, these regress. Only a subset of infected individuals has lesions which progress to high grade intraephithelial neoplasia and only a fraction of these progress further to invasive carcinoma.

The molecular events leading to HPV infection have not been clearly established. The lack of an adequate *in vitro* system to propagate human papillomaviruses has hampered the progress to a best information about the viral cycle.

Today, the different types of HPVs have been isolated and characterised with the help of cloning systems in bacteria and more recently by PCR amplification. The molecular organisation of the HPV genomes has been defined on a comparative basis with that of the well characterised bovine papillomavirus type 1 (BPV1).

Although minor variations do occur, all HPVs genomes described have at least seven early genes, E1 to E7 and two late genes L1 and L2. In addition, an upstream regulatory region harbors the regulatory sequences which appears to control most transcriptional events of the HPV genome.

E1 and E2 genes are involved in viral replication and transcriptional control, respectively and tend to be disrupted by viral integration. E6 and E7 are involved in viral transformation. E5 has also been implicated in this process.

In the HPVs involved in cervical carcinoma such as HPV 16 and 18, the oncogenic process starts after integration of viral DNA. The integration results in the inactivation of genes coding for the capsid proteins L1 and L2 and loss of E2 repressor function leads to deregulation of the E6/E7 open reading frame installing continuously overexpression of the two early proteins E6 and E7 that will lead to gradually loss of the normal cellular differentiation and the development of the carcinoma. E6 and E7 overcome normal cell cycle by inactivating major tumor suppressor proteins, p53 and pRB, the retinoblastoma gene product, respectively.

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Carcinoma of the cervix is common in women and develops through a pre-cancerous intermediate stage to the invasive carcinoma which frequently leads to death. The intermediate stages of the disease is known as cervical intraepithelial neoplasia and is graded I to III in terms of increasing severity ***(CIN I-III).***

Clinically, HPV infection of the female anogenital tract manifests as cervical flat condylomas, the hallmark of which is the koilocytosis affecting predominantly the superficial and intermediate cells of the cervical squamous epithelium.

Koilocytes which are the consequence of a cytopathic effect of the virus, appear as multinucleated cells with a perinuclear clear haloe. The epithelium is thickened with abnormal keratinisation responsible for the warty appearance of the lesion.

Such flat condylomas when positive for the HPV 16 or 18 serotypes, are high-risk factors for the evolution toward cervical intraepithelial neoplasia (CIN) and carcinoma in situ (CIS) which are themselves regarded as precursor lesions of invasive cervix carcinoma.

The natural history of oncogenic HPV infection presents three consecutive phases, namely:

(1) a latent infection phase,

(2) a phase of intranuclear viral replication with product of complete virions, which corresponds to the occurrence of koilocytes. At this stage, the HPV is producing its full range of proteins including E2, E5, E6, E7, L1 and L2.

(3) a phase of viral integration into the cellular genome, which triggers the onset of malignant transformation, and corresponds to CIN II and CIN III/CIS with progressive disappearance of koilocytes. At this stage, the expression of E2 is down-regulated, the expression of E6 and E7 is enhanced. Between CIN II/III and CIN III / Cervix carcinoma the viral DNA changes from being episomal in the basal cells to integration of E6 and E7 genes only (tumoral cells). 85% of all cervix carcinomas are squamos cell carcinomas most predominantly related to the HPV16 serotype. 10% and 5% are adenocarcinomas and adenosquamos cell carcinomas respectively, and both types are predominantly related to HPV 18 serotype. Nevertheless other oncogenic HPV's exist.

International Patent Application No. WO 96/19496 discloses variants of human papilloma virus E6 and E7 proteins, particularly fusion proteins of E6/E7 with a deletion in both the E6 and E7 proteins. These deletion fusion proteins are said to be immunogenic.

Immunomodulatory oligonucleotides contain unmethylated CpG dinucleotides ("CpG") and are known (WO 96/02555, EP 468520). CpG is an abbreviation for cytosine-guanosine dinucleotide motifs present in DNA. Historically, it was observed that the DNA fraction of BCG could exert an anti-tumour effect. In further studies, synthetic oligonucleotides derived from BCG gene sequences were shown to be capable of inducing immunostimulatory effects (both in vitro and in vivo). The authors of these studies concluded that certain palindromic sequences, including a central CG motif, carried this activity. The central role of the CG motif in immunostimulation was later elucidated in a publication by Krieg, Nature 374, p546 1995. Detailed analysis has shown that the CG motif has to be in a certain sequence context, and that such sequences are common in bacterial DNA but are rare in vertebrate DNA.

It is currently believed that this evolutionary difference allows the vertebrate immune system to detect the presence of bacterial DNA (as occurring during an infection) leading consequently to the stimulation of the immune system. The immunostimulatory sequence as defined by Krieg is:

Purine Purine CG pyrimidine pyrimidine and where the CG motif is not methylated. In certain combinations of the six nucleotides a palindromic sequence is present. Several of these motifs, either as repeats of one motif or a combination of different motifs, can be present in the same oligonucleotide. The presence of one or more of these immunostimulatory sequence containing oligonucleotides can activate various immune subsets, including natural killer cells (which produce interferon γ and have cytolytic activity) and macrophages (Wooldrige et al Vol 89 (no. 8), 1977). Although other unmethylated CpG containing sequences not having this consensus sequence have now been shown to be immunomodulatory.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to vaccine compositions, comprising an E6 or/ and E7 or E6, E7 fusion protein from an HPV strain optionally linked with an immunological fusion partner and formulated with a CpG containing oligonucleotide into vaccines that find utility in the treatment or prophylaxis of human papilloma virus induced tumours or lesions.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1 and 2 illustrate the therapeutic potential of a vaccine containing the PD1/3 E7 fusion protein and different CpG oligonucleotides as assessed by the tumour growth in the TC1 model (E7 expressing tumour model). The mean tumour growth (in mm2)/group n=10 mice) over a period of 4 weeks is represented.

Figures 3 and 4 show the relative percentage of the different IgG isotypes (IgG1, IgG2a, IgG2b, IgGTot) in the total of IgGs as measured by ELISA, 2 and 4 weeks post II respectively. Group 1 received PBS, group 2 received ProtD1/3 E7 HPV16, group 5 received ProtD1/3 E7 HPV16 + oligo 1, group 6 received Oligo 1, group 7 received ProtD1/3 E7 HPV16 + oligo 2 and group 8 received Oligo 2.

Figure 5 illustrates the tumour regression as measured by the mean tumour growth (per group of 5 animals) in animals immunised with a vaccine containing the PD1/3 E7 fusion protein and different phosphorothioate modified CpG oligonucleotides. 10e6 TC1 cells were injected subcutaneously (200µl) in the flank of immunocompetent C57BL/6 mice, mice have been vaccinated twice intra- footpad (100 µl : 50µl / footpad), 7 and 14 days after the tumour challenge, with 5µg ProtD 1/3 E7 HPV16.

Figure 6 shows that therapeutic vaccination with CpG oligonucleotide and PD1/3 E7 fusion protein results in a reduction of tumour growth and can induce complete tumour regression, as assessed in the transgenic mice expressing E7 protein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions comprising either an E6 or/and E7 or an E6/E7 fusion protein optionally linked to an immunological fusion partner having T cell epitopes, and adjuvanted with an immunomodulatory CpG containing oligonucleotide.

In particular, the present invention relates to vaccines comprising fusions proteins, comprising a protein or part of a protein that provides T helper epitopes (such as protein D from Heamophilus influenzae B) and an antigen from a human-papilloma virus (eg comprising an E6 or E7 protein from HPV 16 or 18 strain associated with cancer) that find

utility in the treatment or prophylaxis of human papilloma induced tumours, wherein the vaccine is formulated with a CpG containing oligonucleotide as an adjuvant.--

IN THE CLAIMS:

Claims 1-5, 7-9, and 15-16 have been amended as follows:

1. (Amended) A composition comprising an E6 or E7 protein or E6/E7 fusion protein from HPV optionally linked to an immunological fusion partner having T helper epitopes, and an [immunomodulatory] immunostimulatory CpG oligonucleotide containing an unmethylated CpG dinucleotide.

2. (Twice Amended) A composition as claimed in claim 1 wherein the fusion partner is selected from the group consisting of: protein D or a fragment thereof having T helper epitopes from Heamophilius influenzae B, lipoprotein D or fragment thereof having T helper epitopes from Heamophilius influenzae B, NS1 or fragment thereof having T helper epitopes from Influenzae Virus, and LYTA or fragment thereof having T helper epitopes from Streptococcus Pneumoniae.

3. (Twice Amended) A composition as claimed in claim 1 wherein the E6 or E7 proteins are [derived] from HPV16 or HPV18.

4. (Twice Amended) A composition as claimed in claim 1 wherein the E7 protein is mutated to reduce the binding for the retinoblastoma gene product.

5. (Twice Amended) A composition as claimed in claim 1 wherein a mutation is introduced into the E6 protein [is mutated] wherein inactivation of the p53 tumour suppressor protein by E6 is eliminated.

7. (Twice Amended) A composition as claimed in claim 1 further comprising an additional HPV antigen wherein the additional HPV antigen is one or more antigens selected from the group consisting of E2, E5, L1 and L2.

8. (Twice Amended) A composition as claimed in claim 1 wherein the [immunomodulatory] immunostimulatory CpG oligonucleotide comprises a hexamer motif: purine purine cytosine guaine pyrimidine pyrimidine.

9. (Twice Amended) A composition as claimed in claim 1 wherein the[immunomodulatory] immunostimulatory CpG oligonucleotide has two or more CpG motifs.

15. (Twice Amended) A method of preparing a composition as claimed in claims 1-11 or 16, comprising admixing an E6, E7 or E6/E7 fusion protein optionally linked to an immunological fusion partner having T helper epitopes, and an [immunomodulatory] immunostimulatory CpG oligonucleotide.

16. (Amended) A composition as claimed in claim 6 further comprising an additional HPV antigen wherein the additional HPV antigen is one or more antigens selected from the group consisting of E2, E5, L1 and L2.

The following new claims 17-20 have been added:

17. A composition as claimed in claim 7 wherein L1 and L2 are presented together as a virus like particle or wherein L1 alone is presented as a virus like particle or as a capsomere structure.

18. A method of inducing an immune response in a patient to an HPV antigen comprising administering a safe and effective amount of a composition as claimed in claim 17.

19. A method of preventing or treating HPV induced tumours in a patient comprising administering a safe and effective amount of a composition as claimed in claim 17.

20. A method of preparing a composition as claimed in claim 17, comprising admixing an E6, E7 or E6/E7 fusion protein optionally linked to an immunological fusion partner, and an immunostimulatory CpG oligonucleotide.